

Serum IgE Levels in the Convalescent Phase of Kawasaki Disease: A Correlation with Atopy?

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ABSTRACT

Forty-four children with Kawasaki disease were identified retrospectively from the medical records of the Department of Paediatrics of the University of Hong Kong between 1984 and 1990. Serum IgE levels from 30 of 44 patients with Kawasaki disease were obtained at least 4 months after the acute disease. Histories concerning asthma or eczema were obtained from 39 of 44 children by a standard questionnaire. Two age- and sex-matched normal controls per study case were recruited from the community. Serum IgE and atopic history were similarly obtained from the controls. The serum IgE levels from children in the convalescent phase of Kawasaki disease were significantly higher than that of age- and sex-matched normal controls ($p < 0.02$), with a median serum IgE of 85 IU/ml (range 4–679) for the Kawasaki patients compared to a median of 22 IU/ml for controls (range 1–653). Although we found a higher prevalence of atopy in children with Kawasaki disease when compared with matched controls (20.5% vs 10.3%), this difference was not statistically significant. We conclude that there is a possible link between Kawasaki disease and atopy in Hong Kong children.

INTRODUCTION

KAWASAKI DISEASE is an acute febrile illness occurring in infants and young children. Other features include rash, mucositis, conjunctivitis, change of the extremities, and the presence of cervical lymphadenopathy.^(1,2) The etiology of Kawasaki disease is still not known, but immunologic abnormalities have been detected in children during the acute phase of the disease, including increased activation of T helper cells,⁽³⁾ increased interleukin 1 (IL-1),⁽⁴⁾ tumor necrosis factor (TNF),⁽⁵⁾ and soluble interleukin 2 receptor (IL-2R) levels,⁽⁶⁾ and a transient increase in immunoglobulin levels.⁽⁷⁾ Some of the immunologic derangements are shared by patients with atopic dermatitis, including elevated IgE levels⁽⁸⁾ and decreased numbers of circulating suppressor T cells.⁽⁹⁾ A higher incidence of atopic dermatitis as well as increased convalescent IgE

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levels have been observed in children with Kawasaki disease.⁽¹⁰⁾ Atopy is a common observation in Hong Kong children, and the most common allergen has been identified as the house dust mite (86.7% of atopic children in Hong Kong have IgE specific for *Dermatophagoides pteronyssinus*, unpublished observations). These mites are a vector for *Propionibacterium acnes*, which has been implicated as a possible etiologic agent for Kawasaki disease.⁽¹¹⁾ Thus, we have undertaken to ascertain if there is an association between Kawasaki disease and atopy in Hong Kong, by a case-control study comparing serum IgE levels and the prevalence of clinically apparent asthma or eczema between children with a history of Kawasaki disease and normal controls.

MATERIALS AND METHODS

Patients

Forty-four Chinese children with Kawasaki disease admitted to Queen Mary Hospital or Grantham Hospital between 1948 and 1990 were retrospectively identified from the hospital records. All children with Kawasaki disease met the Japan Kawasaki Disease Research Committee guidelines for diagnosis (4th version).⁽¹²⁾ Parents of 39 of these children were contacted successfully for determination of IgE levels and completion of a questionnaire regarding history of atopy. The parents of 27 children consented to have serum drawn for IgE titers at least 4 months after the onset of illness. History regarding the presence or absence of eczema or asthma was obtained from all 39 patients contacted. Eczema was defined as a chronic, pruritic skin eruption marked by erythema and papules. Asthma was defined as recurrent wheezing attacks. The remaining 5 patients were lost to follow-up. However, 3 of these 5 had had convalescent titers of total serum IgE drawn previously. The IgE levels of these 3 patients were incorporated into the study.

Controls were healthy Chinese children who were either attending a Maternal and Child Health Clinic for vaccination or studying in a kindergarten, who participated in a survey to establish normal immunoglobulin levels in Chinese children. Approval was obtained from the Ethics Committee for the survey. There was no history of serious illness or recurrent infections in these children. IgE levels were drawn, and a standard questionnaire regarding history of eczema and asthma in these children was completed. Two age-matched (to the nearest 9 months) and sex-matched controls for each child with Kawasaki disease were selected at random without prior knowledge of serum IgE levels or atopic history.

IgE determination

Serum IgE was determined using Abbott's enzyme immunoassay (EIA). We previously have determined the interassay variation of this test to be less than 10%.

Statistics

Since the distribution of IgE levels in the two groups was skewed, they were compared by nonparametric Mann-Whitney U test using MINITAB on an IBM computer. Chi-square analysis was used to determine if there was a significant difference in the prevalence of atopy in children with Kawasaki disease compared with controls. Level of significance was taken to be $p < 0.05$.

RESULTS

The mean age of subjects with Kawasaki disease at the time of determination of convalescent IgE titers was 48.3 months (compared with 48.9 months in the control group). Figure 1 shows the distribution of IgE levels in the two groups. The median IgE level for the patients with Kawasaki disease was 85 IU/ml (range 4–679), compared with 22 IU/ml (range 1–653) for controls. The IgE levels in the Kawasaki disease patients were determined to be significantly higher than those of the control group by the Mann-Whitney U test ($p < 0.02$).

SERUM IgE IN CONVALESCENT KAWASAKI DISEASE

Eight of a total of 39 patients (20.5%) with Kawasaki disease had a history of asthma or eczema, compared with 8 of 78 controls (10.3%), (Chi-square = 2.31, $p > 0.05$). The data are summarized in Table 1.

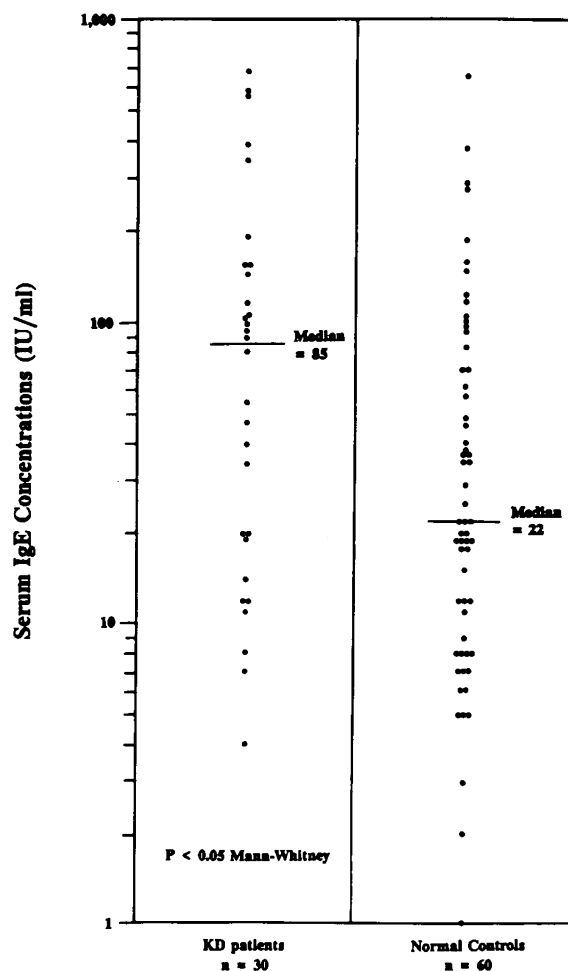


FIG. 1. Serum IgE concentrations in 30 patients at least 4 months after the onset of Kawasaki disease compared with IgE concentrations in 60 age- and sex-matched normal controls. IgE concentrations were significantly higher in the Kawasaki disease group than in the control group ($p < 0.02$ Mann-Whitney U test).

DISCUSSION

Kusakawa and Heiner⁽⁷⁾ demonstrated a two- to fourfold elevation of total serum IgE during the acute phase of Kawasaki disease, reaching a peak 1–2 weeks after onset. The IgE level would then decline over the ensuing 1–2 months. However, the convalescent IgE level taken at a mean of 32.9 days after the onset was not significantly higher than that of controls. On the other hand, Brosius et al.⁽¹⁰⁾ showed a significant increase in

TABLE 1. ASSOCIATION BETWEEN PREVALENCE OF ATOPY IN CHILDREN WITH KAWASAKI DISEASE VS CONTROLS

	<i>Kawasaki patients</i>	<i>Controls</i>	<i>Totals</i>
Atopy	8	8	16
No atopy	31	70	101
Totals	39	78	117 ^a

^aChi-square = 2.31, $p > 0.05$.

convalescent IgE level taken at 6 months after onset in a larger group of children with Kawasaki disease as compared to controls, which agreed with our findings. The increase in IgE levels 4–6 months after onset of the disease is probably not due to the transient polyclonal B cell stimulation resulting from increased numbers of activated T helper cells observed during the acute phase of Kawasaki disease, since the serum half-life of IgE is only 2–3 days.⁽¹³⁾ The increase in serum IgE is consistent with our observation that patients with Kawasaki disease have an increased prevalence of atopy. However, it is impossible to exclude the possibility that Kawasaki disease causes a persistent change in the regulation of IgE production because the serum IgE was not measured before disease onset. The presence of confounding variables, such as race, age, and sex, has been accounted for in this study, but additional confounders may be important. In particular, since the IgE level in atopic individuals may vary with the presence or absence of allergen in the environment, differences in the season in which the sera were obtained may affect the results of the two groups. This potential source of error has been minimized, since all sera in both groups were drawn between May and September of either 1989 or 1990.

Establishing an association between Kawasaki disease and clinical atopy is more difficult. In our study, the diagnosis of eczema or asthma was not determined by physical examination in either the Kawasaki patient group or the control group but rather by a standard questionnaire. Moreover, the questionnaire used in the two groups was not exactly the same, and a bias could be introduced by the better recall of parents of children with Kawasaki disease as compared to parents of normal children. As the difference in prevalence of atopy in Kawasaki disease and normal controls was not found to be statistically significant in this study, we failed to establish unequivocally a link between Kawasaki disease and atopy. However, such a link has been shown previously by a similar case-control study.⁽¹⁰⁾ IgE levels in atopic Asian children are generally higher than those of Caucasians.⁽¹⁴⁾ Similarly, Kawasaki disease is seen more frequently in some Asian populations, particularly Japanese.⁽¹⁵⁾ This suggests a genetic predisposition to both conditions. Further prospective studies may help determine if this increase in the prevalence of atopy is a universal finding in Kawasaki disease patients in all areas of the world.

Interestingly, one of the infectious agents implicated as an etiologic agent for Kawasaki disease, *Propionibacterium acnes*,⁽¹¹⁾ is carried by the common house dust mite, which has been found to be the major allergen responsible for IgE elevation and clinical atopy in Hong Kong children (unpublished observations). Although *P. acnes* is a common skin organism,⁽¹⁶⁾ children with Kawasaki disease have been shown to have increased antibody to a cytopathogenic protein (CPP) of *P. acnes*. Although these relationships may be coincidental, it may also suggest that children who are predisposed to developing an allergic reaction to *D. pteronyssinus* may also be more apt to develop some derangement in immunologic modulation in response to some as yet unidentified epitope of *P. acnes*. In acute rheumatic fever, the group A *Streptococcus* carries a polysaccharide that crossreacts with a glycopeptide on the heart valves, possibly resulting in an autoimmune response leading to damage of the valves.^(17,18) A similar mechanism may be involved in the pathogenesis of Kawasaki disease, and it would be interesting to see if there are similarities in immunologic properties between *P. acnes* and the endocardium in Kawasaki patients who develop coronary aneurysms. Unfortunately, a correlation between the occurrence of coronary aneurysms and the preexistence of atopy in Kawasaki disease patients could not be established in our study because of the small numbers.

SERUM IgE IN CONVALESCENT KAWASAKI DISEASE

In summary, striking immunologic and clinical similarities have been shown previously between patients with atopy and patients with acute Kawasaki disease.^(3,8-10) Now it is apparent that IgE levels remain elevated long after the acute phase of this illness. Studies on immune response genes by HLA typing^(19,20) or T cell receptor gene polymorphism⁽²¹⁾ may shed light on whether there may indeed be some similar genetic predisposition of immunologic response in Kawasaki disease and atopy.

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